CLINICAL EVALUATION OF THE RESULTS OF THE SECRETIN TEST AND OF DUODENAL CYTOLOGY IN THE DIAGNOSIS OF PANCREATIC DISEASE

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THE early diagnosis of pancreatic disease remains a challenging and perplexing problem. Clinical signs and symptoms may be minimal or misleading in the presence either of inflammatory or of neoplastic disease. The retroperitoneal location of the pancreas renders it almost inaccessible to the usual methods of physical diagnosis, except in instances of large carcinomatous masses and pancreatic cysts. Even at operation, carcinoma of the pancreas may be difficult to diagnose unless there are metastatic nodes. Some surgeons are reluctant to biopsy the pancreas, even with the Vim-Silverman or the Menghini needle, because of the possibility of producing a pancreatic fistula; others believe that needle biopsy is a safe procedure, particularly when it is done transduodenally. However, the findings on needle biopsy may be negative for neoplasm, even when a neoplasm is present. Since pancreatitis may simulate carcinoma, the diagnosis can be proved only by a study of pathologic sections.

An early diagnosis of carcinoma of the pancreas is essential for successful surgical treatment, which is the only hope for a cure available now. An accurate diagnosis of neoplasm of the pancreas is also helpful in the medical treatment of the patient, in the prognosis, and in discussions with the family regarding treatment and prognosis. All possible means of treatment are indicated, because the outcome is always in doubt. However, in cases of neoplasm of the pancreas, with its poor prognosis, extensive efforts may prolong life only for a few hours or days.

The symptoms of carcinoma of the pancreas are usually vague and nonspecific. Pain in the back and persistent or shifting abdominal pain are frequent symptoms. Loss of weight and indigestion occur. Mental depression may be a manifestation of carcinoma of the pancreas. Jaundice is commonly a late manifestation of carcinoma of the head of the pancreas. The symptoms of pancreatic carcinoma may be the same as those of functional indigestion or chronic irritable colon, or they may simulate those of a gastrointestinal or a conversion neurosis. However, the patient with a neurosis or chronic irritable colon usually has had similar distress for many years, while the patient with a carcinoma of the pancreas has had symptoms for a relatively short period. In a patient more than 50 years of age, the sudden onset of vague indigestion, back pain, abdominal pain (shifting or in the same location), loss of appetite or loss of weight, mental depression, and symptoms suggestive of functional indigestion, or chronic irritable colon, or of a conversion neurosis, should suggest the possibility of carcinoma of the pancreas. The short duration of symptoms in an

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elderly patient who previously had been well, is the most important sign of pancreatic neoplasm.

Tests of pancreatic function available a decade ago were primarily tests of intestinal absorption; the results were abnormal only when extensive pancreatic disease was present, and late in its course. With a decrease in pancreatic function, the production of fat-splitting lipases is inadequate, resulting in malabsorption of neutral fats and steatorrhea. Quantitative analysis of the stool for fat shows an excess amount; Henke and associates[1] found that 20 (64.5 percent) of 31 patients with chronic pancreatitis had excess fat in the stool. The absorption of I^{131}-labeled triolein is impaired, while that of I^{131}-labeled oleic acid (a simple fatty acid requiring the action of no digestive enzymes) is normal. In addition to abnormal absorption caused by lack of pancreatic enzymes, pancreatic disease may cause diabetes. The finding of previously undiagnosed diabetes in a patient having no family history of diabetes, but having abdominal pain or some of the other typical symptoms of pancreatic disease, should suggest the diagnosis of pancreatic carcinoma or pancreatitis. Unfortunately in terms of early diagnosis, steatorrhea and diabetes are late manifestations of pancreatic disease.

Although Bayliss and Starling[2] first discovered secretin in 1902, it was not available commercially for clinical studies until 1953. Thus, since 1953, and the availability of secretin commercially, there has been growing interest in the sensitive tests of pancreatic function in the diagnosis of pancreatic disease. The effects of pancreatic stimulation by secretin and pancreozymin on the volume and the bicarbonate concentration of pancreatic secretion, and on the serum amylase and lipase concentrations, and the results of cytologic examinations of the duodenal contents for malignant cells have been reported.[3-6] For the last three years we have been using the secretin test and duodenal cytology in an attempt to evaluate these time-consuming procedures in the practical clinical diagnosis of pancreatic disease.

The pancreatic response to secretin can be affected by lesions that obstruct the flow of secreted juice, or by a pathologic process that injures the secreting cells. The extent of defect in secretion caused by pancreatic neoplasms depends upon the site and degree of obstruction of the pancreatic duct. Thus, after stimulation with secretin, there is a quantitative reduction in volume of pancreatic secretion: extreme for lesions in the head, which block the response of almost the entire gland; moderate for lesions of the body, which obstruct secretion from only half of the gland; and negligible for lesions of the tail, which can obstruct only an insignificant portion of the secreting parenchyma.

In contrast to this quantitative (volume) secretory defect in pancreatic cancers, decrease in the secretion of pancreatic enzyme (qualitative defect) is diagnostic for chronic pancreatic inflammation. In chronic pancreatitis, a relative preservation of volume flow of pancreatic secretion in response to secretin is coupled with the inability to elaborate a juice of high bicarbonate concentration and high enzyme content.

There may be overlapping between the findings in patients having severe long-standing chronic pancreatitis, in which there are both quantitative and qualitative defects because of massive obstruction of parenchyma, and the findings in patients having cancer of the head of the pancreas involving the main duct at or near its origin, in which the same combined quantitative and qualitative defects occur because practically no pancreatic secretions enter the duodenum after the administration of secretin. It is in these cases that the additional findings on the exfoliative cytologic examination of the duodenal secretion have been of help in making a definite diagnosis.

Cytologic study of the duodenal drainage has been combined with the secretin test to determine the accuracy of the test, especially in those cases which are most difficult to diagnose: namely, cancer of the tail of the pancreas, preexisting chronic pancreatitis associated with a neoplasm, and when the findings are consistent either with neoplasm or with severe chronic pancreatitis.

Material and Method

A consecutive series of 240 patients was studied, 19 of whom were proved subsequently to have carcinoma of the pancreas. The diagnosis of pancreatitis was established in 31 patients, either by roentgen evidence of pancreatic calcification or by biopsy.

A total of 250 secretin studies was performed on the 250 patients. The material obtained by duodenal aspiration after the injection of secretin was analyzed for total volume and for bicarbonate concentration. In addition, two aliquots of each duodenal drainage were sent to the laboratory for cytologic examination. The normal values for duodenal contents in response to secretin are based on the range in 25 normal subjects. These values are a total volume response of more than 150 ml. per hour, and a maximum bicarbonate concentration of more than 85 mEq. per liter.

Fasting and two-hour poststimulation serum lipase and amylase determinations were done. The serum amylase concentrations were determined by the method of Myers, Free, and Rosinski,[7] and the serum lipase by the method of Johnson and Bockus.[8]

The technic described by Raskin and associates,[9] for rapid intubation of the duodenum was in general followed. The radiopaque double-lumen tube was passed into the duodenum under fluoroscopic control, in the fasting patient. The technic of the secretin test is described by Dreiling.[10] With the double-lumen tube in the duodenum, a 20-minute control specimen of material is collected. Then, 80 units of secretin (Boots) is injected intravenously, and four specimens of the duodenal contents are collected at 10, 20, 40, and 60 minutes after the injection. Despite the use of fluoroscopy and the various maneuvers suggested for intubation, the procedure is a time-consuming one. The collection of the specimens and the cytologic examination for neoplastic cells are also time-consuming.

Results and Discussion

Pancreatic carcinoma

Dreiling,[11] reporting on the use of the secretin test, noted a depression of volume of pancreatic secretion in 52 of 61 patients with proved carcinoma of the pancreas. In three of the remaining patients, the bicarbonate concentrations of the pancreatic secretion were below the normal range. Therefore, there were only 6 of 61 patients having pancreatic carcinomas in whom both the volume and the bicarbonate concentration of pancreatic secretion were normal. Wenger and Raskin,[12] using the secretin test, observed a decreased volume of pancreatic secretion in 20 of 32 patients having pancreatic carcinoma, the other 12 had normal volumes of secretions. In addition, 20 of these patients showed a reduction of bicarbonate concentration, presumably resulting from a rather diffuse involvement of the gland with the neoplastic process.

Our series, as stated, included 19 patients with proved carcinoma (*Table 1*). Of

Table 1.—*Results of secretin tests in 19 patients with carcinoma of the pancreas*

Results		No. of patients
Normal values		2
Abnormal values		17
One test only	3	
Two or more tests	14	
Positive cytologic findings		7
Low bicarbonate concentrations		14
Low volumes		10
Low bicarbonate concentrations and low volumes		8

this group, 7 (37 percent) had positive cytologic findings. In 10 (53 percent), the volume of pancreatic secretion was low, and in 14 (73 percent) the bicarbonate concentration was low. A total of eight (43 percent) had both low volume and low bicarbonate concentration, whereas in only two patients were both the values normal. Of the 12 patients with negative findings on cytologic studies, seven had both low volume and low bicarbonate concentration. Fourteen patients (79 percent) had two or more abnormal results of tests consistent with the diagnosis of pancreatic neoplasm.

Pancreatitis

Dornberger and associates,[13] in 65 of 68 patients, and Dreiling,[14] in 70 of 72 patients, all with chronic pancreatitis, found the total volume and maximum bicarbonate concentration of the duodenal content to be abnormal after injection of secretin. Dreiling[14] in the same series found abnormal values in 22 of 48 patients

with acute pancreatitis. He concluded that the secretin test had limited practical value in the diagnosis of acute pancreatitis. In our series we included no patients who had only a single attack of acute pancreatitis.

It has been shown many times that a large portion of the pancreas can be compromised without altering its secretory function, indicating that the pancreas has a tremendous functional reserve. Sun and Shay[15] reported a case in which after a partial pancreatectomy and subsequent damage to the remaining portion of the pancreas, the responses to the secretin test were normal: serum enzyme concentration, volume and bicarbonate concentration of pancreatic secretion in the duodenal contents were all normal. Although an abnormal response to stimulation with secretin indicates severe pancreatic disease, a normal response does not exclude the possibility of disease.

In the present series, 31 patients were subsequently found to have chronic pancreatitis (*Table 2*). Twenty-seven (87 percent) of these had significantly de-

Table 2.—*Results of secretin tests in 31 patients with chronic pancreatitis*

Results	No. of patients	
Normal values		2
Abnormal values		29
One test only	16	
Two or more tests	13	
Low bicarbonate concentrations		27
Low volumes		10
Low bicarbonate concentrations and low volumes		8
Elevated serum amylase and lipase values		7

creased bicarbonate concentration, and 10 (32 percent) had a low total volume of pancreatic secretion. A total of eight (26 percent) had both low volume and low bicarbonate concentration. There were only two (7 percent) with entirely normal values.

From these findings, it can be concluded that changes in the volume or bicarbonate concentration of pancreatic secretion, or decreases in both, did not differentiate pancreatitis from pancreatic neoplasm. Abnormalities in volume and bicarbonate concentration of pancreatic secretion indicated only pancreatic disease, without indicating the type of disease.

Secretin is known to be a potent stimulus to bicarbonate concentration, but does not affect the rate of enzyme formation. Several studies have been reported in which pancreozymin, in addition to the secretin, has been used in order to produce an augmented enzyme response. The attempt to produce increased enzyme response

has been made because of the fact that in many series[16-18] reported, serum enzyme values in normal subjects after secretin stimulation were below the upper limits of normal. It was generally agreed, therefore, that a response was considered to be positive only when serum enzyme values of the pancreatic stimulation with secretin were above the upper limits of normal. We found the serum amylase and lipase determinations after injection of secretin to be of little value diagnostically; serum amylase concentration was elevated in 7 of the 31 patients with chronic pancreatitis.

Two patients had reactions to secretin. In one, urticaria and hives developed; and in the other acute cholecystitis developed within eight hours after the injection.

Exfoliative cytology

The pancreas and biliary tract have been most challenging and intriguing regions for the cytologist. Reports of the findings on pancreatic exfoliative cytology are few. Lemon and Byrnes,[19] who summarized their five-year experiences, identified malignant cells cytologically in 13 of 36 patients who were proved to have a primary cancer of the liver, pancreas, or biliary tract, a diagnostic accuracy of 36 percent. Raskin, Kirsner, and Palmer[20] reported that of 55 patients with proved pancreatic carcinoma, malignant cells were recovered by duodenal drainage in 33 patients, a diagnostic accuracy of 60 percent. Raskin and associates[21] believe generally that the larger the pancreatic tumor the less likelihood there is for recovery of malignant cells, as invariably there is an obstruction of the main pancreatic duct.

Of our total group of 240 patients, there were 16 with positive cytologic findings, 7 (44 percent) of whom proved to have pancreatic cancer (*Table 3*). In each

Table 3.—*Cytologic findings in 240 patients*

Diagnosis	Positive	Negative	Total no. of patients
Carcinoma of the pancreas	7	12	19
Other neoplasms	4	—	4
Chronic pancreatitis	3	28	31
No pancreatic or neoplastic disease	2	184	186
Totals	16	224	240

of these patients, the disease was found to involve the head and/or the body of the pancreas; in two patients, the tail was involved as well. These findings are consistent with those reported for other series. Four (25 percent) patients with positive cytologic findings were each found to have a neoplasm other than pancreatic: two with gastric cancer and one each with metastatic colonic cancer and multiple myeloma. There were five (31 percent) who had false-positive tests, a percentage of 2.2 percent among 221 patients who did not have pancreatic neoplasms. Included

in these, were three with chronic pancreatitis, all of whom had abnormally low bicarbonate concentrations but normal volumes of pancreatic secretion.

The cytologic differentiation of malignant cells from inflammatory cells in patients who have pancreatitis may be difficult. A fourth patient with false-positive cytologic findings had a penetrating duodenal ulcer.

The number and percentage of false-positive cytologic findings are small. Nonetheless, the fact that false-positive results did occur indicates that complete reliance cannot be placed on the cytologic findings alone, and that the cytologic results must be correlated with the entire clinical picture in each patient.

Summary

Studies of the pancreatic secretion after duodenal intubation and stimulation of the pancreas with injections of secretin were done in 240 patients, 19 of whom proved to have carcinoma of the pancreas, and 31 of whom proved to have chronic pancreatitis. The material obtained was studied for volume of pancreatic secretion, bicarbonate concentration, and enzyme values, and was examined cytologically.

Of the 19 patients with carcinoma of the pancreas in our series, 17 had at least one abnormal value, and 14 had two or more. Of the 31 patients with chronic pancreatitis, 13 had two or more abnormal values, and 29 had at least one abnormal value. Cytologic findings were positive in 16 of the 240 patients. Eleven of these 16 patients proved to have neoplasm, and 7 of the 11 pancreatic carcinoma. There were five false-positive tests, three in patients with chronic pancreatitis and one in a patient with a penetrating duodenal ulcer.

Of the 50 patients with either carcinoma of the pancreas or chronic pancreatitis, 46 (92 percent) had at least one abnormal finding on the secretin test.

Abnormal pancreatic secretion after administration of secretin indicates pancreatic disease but usually does not indicate the type of disease (i.e., pancreatitis or carcinoma). The procedure is too time-consuming (with intubation, collection of specimens, and laboratory and cytologic study) to be adopted as a routine test. Pancreatic studies may be of some help in diagnosis when there is strong suspicion of pancreatic disease.

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